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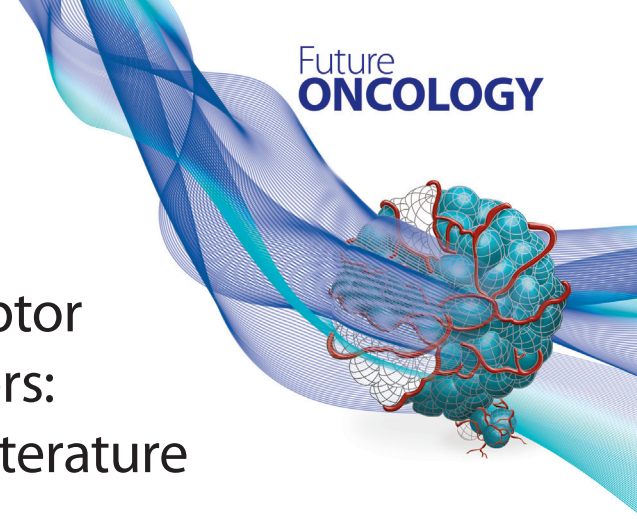

PET tracers for somatostatin receptor imaging of neuroendocrine tumors: current status and review of the literature

Camilla Bardram Johnbeck[1], Ulrich Knigge[2] & Andreas Kjær*[,1]

ABSTRACT Neuroendocrine tumors have shown rising incidence mainly due to higher clinical awareness and better diagnostic tools over the last 30 years. Functional imaging of neuroendocrine tumors with PET tracers is an evolving field that is continuously refining the affinity of new tracers in the search for the perfect neuroendocrine tumor imaging tracer. ^{68}Ga-labeled tracers coupled to synthetic somatostatin analogs with differences in affinity for the five somatostatin receptor subtypes are now widely applied in Europe. Comparison of sensitivity between the most used tracers – ^{68}Ga-DOTA-Tyr3-octreotide, ^{68}Ga-DOTA-Tyr3-octreotate and ^{68}Ga-DOTA-l-Nal3-octreotide – shows little difference and expertise on the specific tracer used, and knowledge regarding physiological uptake might be more important than *in vitro*-proven differences in affinity. Using isotopes such as ^{18}F or ^{64}Cu might improve these PET tracers further.

KEYWORDS
• ^{18}F-DOPA • ^{64}Cu-DOTATATE • ^{68}Ga-DOTANOC • ^{68}Ga-DOTATATE • ^{68}Ga-DOTATOC • cancer • molecular imaging • neuroendocrine tumors • PET imaging • somatostatin receptor imaging

Neuroendocrine tumors (NETs) arise from cells with a neuroendocrine phenotype distributed mainly in the lungs (25%) or the gastro–entero–pancreatic (GEP) tract (75%). NETs have been considered to be rare neoplasms, but an analysis from Surveillance, Epidemiology and End Results (SEER) reports a fivefold increase from 1973 (1.09/100,000) to 2004 (5.25/100,000) [1]. For GEP NETs alone, there has been an increase in the age-adjusted incidence by 3.6-fold in the USA and by 3.8–4.8-fold in Europe from 1973 to 2007 [2]. The awareness of clinicians regarding NETs combined with better diagnostic tools has played a great part in this increasing incidence. Furthermore, the definition of NETs has changed so that benign NETs are now included [3].

NETs can occur throughout the human body in virtually every organ and the tumors are classified according to the organ of origin and by TNM classification [4]. Furthermore, a more universal grading system into G1, G2 and G3 tumors based on Ki67 or the mitotic index (≤2, 2–20 and >20%, respectively) has been proposed by Rindi and colleagues [1,5–6] and is now included in the latest consensus guidelines from European Neuroendocrine Tumor Society (ENETS) and the WHO, at least for GEP NET.

Above the diaphragm, the WHO classification system from 2004 divides lung NETs into four categories based on histological subtypes: the typical carcinoids, the atypical carcinoids, the small-cell carcinomas and the large-cell carcinomas [7]. Recently, however, Rindi *et al.* have suggested a three-tier grading system based on the proliferation index and the amount of necrotic cells, since this distinction also seems to be more clinically relevant in pulmonary NETs [8].

A unique feature of NETs is their overexpression of somatostatin receptors on the tumor cells, which has established the basis for both pharmacological treatment with analogs [9–11] and for

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imaging, as well as peptide receptor radionuclide therapy (PRRT) by radiolabeled targeting of these receptors. Somatostatin receptors are G-protein-coupled membrane glycoproteins, and so far, five subtypes of human somatostatin receptors have been identified: sst1–sst5 [12]. GEP NETs are found to express somatostatin receptors in 80–100% of cases, although insulinomas have a lower prevalence (50–70%) [13,14]. Most abundant is sst2 [15], followed by equal amounts of sst1 and sst5, lower amounts of sst3 and hardly any sst4 [14–16]. In total, 70–90% of NETs express sst2 [17].

The first available somatostatin analog was octreotide, a synthetic octapeptide that exhibited more selective high-affinity binding for sst2 and sst5 and, to a lesser degree, sst3 [18]. Altering small parts of the synthetic peptides readily changes the binding profile to different receptors. Lanreotide and pasireotide are newer long-acting somatostatin analogs that were developed in order to refine clinical effects and gain a broader affinity profile [10]. Furthermore, in the development of tracers for the molecular imaging of NETs, synthetic somatostatin analogs have played a crucial role.

Somatostatin receptor imaging

In 1989, the first somatostatin receptor scintigraphies were performed using ^{123}I-Tyr^{3}-octreotide [19]. One-thousand patients were scanned using γ-camera-based scintigraphy, and a sensitivity of 80–95% was found for carcinoids and endocrine pancreatic tumors [20].

For many years, the radiopharmaceutical of first choice for the visualization of NETs has been ^{111}In-pentreotide, and in the USA, this remains the case. ^{111}In radioisotopes emits γ-radiation and thus imaging is obtained by either planar or tomographical γ-cameras, such as single photon emission computed tomography (SPECT). PET-based radioisotopes such as ^{18}F, ^{68}Ga and ^{64}Cu emit positrons. When the positrons annihilate with an electron, two photons are emitted in opposite directions, and these are detected by the PET scanner.

Combinations with new chelators and PET isotopes have made somatostatin receptor imaging even more sensitive. In general, the sensitivity and resolution is better for PET scanning than for SPECT. Moreover, the quantitative nature of PET makes it possible to quantify the amount of tracer uptake expressed as standardized uptake values (SUVs). The SUVs are very useful in the planning of PRRT and may contain prognostic information [21].

Several studies have determined that PET tracers possess major advantages compared with the γ-emitting tracers, both in terms of detection rates and clinical impact [22–27]. Furthermore, the PET examination takes only a few hours instead of 2–3 days and the costs are also reduced because supplementary MRI or computed tomography (CT) scanning is needed less often [28].

In the European consensus guidelines of ENETS from 2012, SPECT/CT scanning using ^{111}In-DTPA-octreotide (DTPA-OC) is an important part of the diagnostic work-up of patients with NETs. However, a change towards the PET-based tracers is preferred whenever possible [29–32], especially for patients with colonic NETs, insulinomas and multiple endocrine neoplasia syndromes [33,34].

Somatostatin receptor PET tracers

Labeling peptides moved a step forward with the introduction of 1,4,7,10-tetraazacyclodecane-1,4,7,10-tetraacetic acid (DOTA), a universal chelator capable of forming stable complexes with radiotracers of the metal group, such as ^{111}In, ^{67}Ga, ^{68}Ga, ^{64}Cu, ^{90}Y and ^{177}Lu [29]. Peptides labeled with ^{90}Y and ^{177}Lu are used for radionuclide therapy, while most somatostatin receptor imaging tracers use ^{68}Ga as the radioisotope. This isotope has the advantage of being produced from a generator, so it is also available in departments without a cyclotron.

The receptor affinity, radiation type, duration and positron range of the emissions are all of crucial importance for the efficacy of a PET tracer, both in imaging and radionuclide therapy. Even small modifications in the amino acid sequences, as well as conjugation to a chelator and the choice of isotope, may lead to changes in the affinity towards different receptors [22,35]. A change from antagonistic to agonistic behavior has even been described after conjugation to the DOTA chelator [36]. Somatostatin receptor internalization appears to be inducible only by somatostatin agonists and not antagonists [37,38]. Internalization of the receptor–ligand complex has been considered to be necessary for imaging and radionuclide therapy; however, preclinical studies have shown that antagonists bind to more receptor sites than agonists and dissociate more slowly, leading to a strong and possibly long-acting radiation signal [39,40]. A single clinical study has compared ^{111}In-DTPA-octreotide and

an antagonist tracer ^{111}In-DOTA-pNO$_2$-Phe-c(DCys-Tyr-DTrp-Lys-Thr-Cys)DTyrNH$_2$(BASS) in five NET patients. The antagonist tracer found more lesions and showed up to four-times higher tumor uptake of the tracer [41]. In spite of this, the agonist somatostatin analogs are so far the only ones that are used in clinical routine.

The principle of combining radioisotopes, chelators and somatostatin analogs is shown for the most commonly used tracers in **Figure 1**.

The most frequently used modifications of octreotide are Tyr^3-octreotide, Tyr^3-octreotate and l-Nal^3-octreotide. When combined with the DOTA chelator and ^{68}Ga, they are called ^{68}Ga-DOTA-Tyr3-octreotide (^{68}Ga-DOTATOC), ^{68}Ga-DOTA-Tyr3-octreotate (^{68}Ga-DOTATATE) and ^{68}Ga-DOTA-l-Nal3-octreotide (^{68}Ga-DOTANOC). Furthermore, combinations using somatostatin analogs coupled to ^{64}Cu has been reported by a few centers [42,43].

Somatostatin receptor tracer affinity

The binding to the relevant somatostatin receptors is the most crucial factor for the efficacy of imaging with somatostatin receptor tracers. The results of *in vitro* binding studies of the most used somatostatin receptor PET tracers are shown in **Table 1**.

The highest affinity was found for Ga-DOTATATE towards the most abundant receptor sst2. Reubi *et al.* determined the binding affinity of Ga-DOTATATE towards sst2 to be approximately tenfold higher than that of both Ga-DOTANOC and Ga-DOTATOC [35]. Ga-DOTATATE (and In-DTPA-octreotide) only binds to sst2, while Ga-DOTATOC, Ga-DOTAOC and Ga-DOTANOC also binds to sst5. Ga-DOTANOC had a tenfold higher affinity than Ga-DOTATOC and additional binding capacity towards sst3 [35,44]. The somatostatin analog lanreotide has been claimed to be a universal somatostatin receptor agonist, but affinity studies of lanreotide coupled to the DOTA chelator only show relevant affinity for sst2 and sst5 [35]. The affinity measurements were made *in vitro* in cells transfected with the five types of somatostatin receptors. Differences may therefore occur *in vivo*.

• Influence of the chelator & radionuclide

So far, it has mainly been ^{68}Ga that has been used as the radioisotope in somatostatin receptor PET

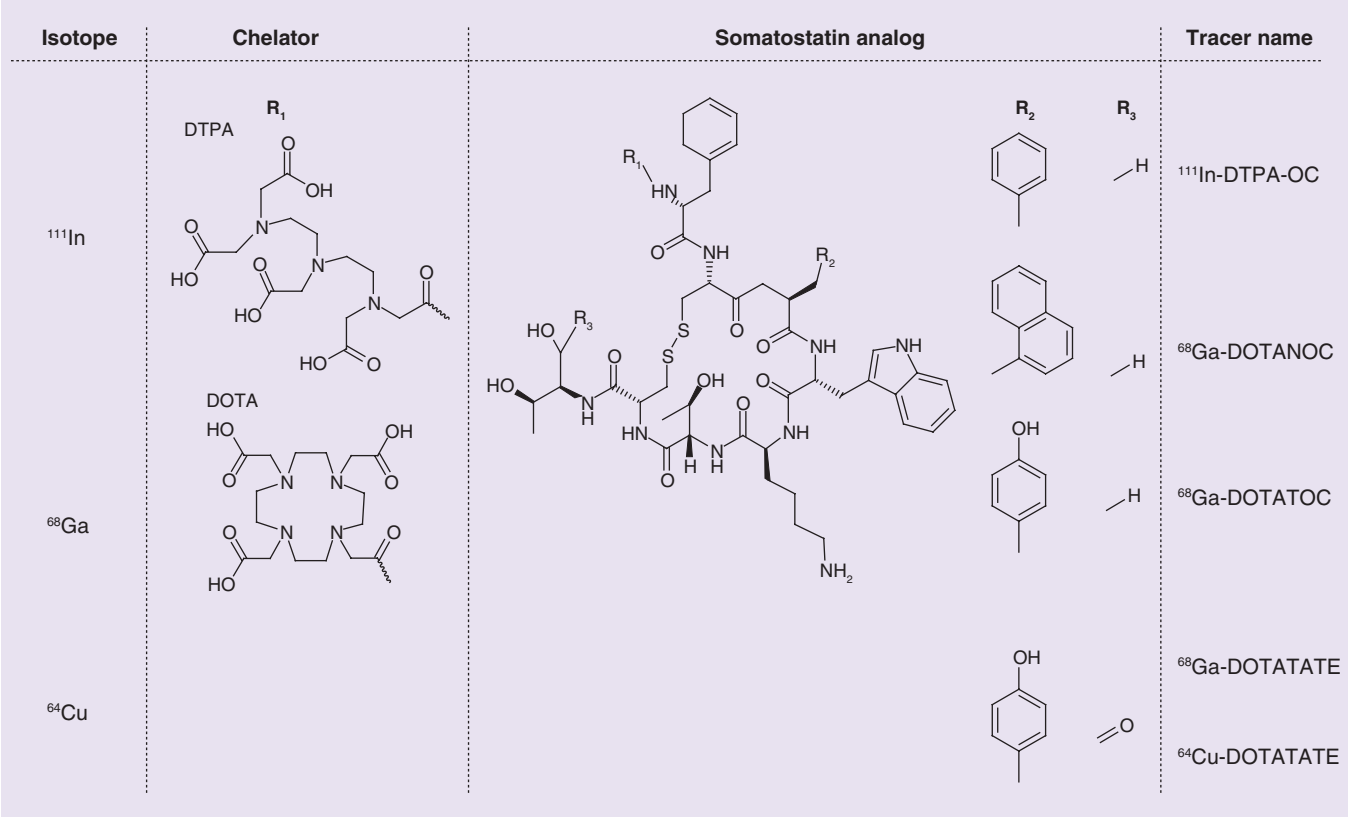

Figure 1. The chemical structure of somatostatin receptor tracers: isotope plus chelator plus somatostatin analog.

Table 1. *In vitro* binding affinity (IC_{50} in nM ± standard error of the mean) of chelated somatostatin analogs.

Somatostatin analog	Name	sst1	sst2	sst3	sst4	sst5
Ga-DOTA-Tyr^3-octreotate	Ga-DOTATATE	>10,000	0.2 ± 0.04	>1000	300 ± 140	377 ± 18
Ga-DOTA-Tyr^3-octreotide	Ga-DOTATOC	>10,000	2.5 ± 0.5	613 ± 140	>1000	73 ± 21
Ga-DOTA-octreotide	Ga-DOTAOC	>10,000	7.3 ± 1.9	120 ± 45	>1000	60 ± 14
Ga-DOTA-l-Nal^3-octreotide	Ga-DOTANOC	>10,000	1.9 ± 0.4	40 ± 5.8	260 ± 74	7.2 ± 1.6
DOTA-lanreotide	DOTALAN	>10,000	26 ± 3.4	771 ± 229	>10,000	73 ± 12
In-DTPA-octreotide	In-DTPA-OC	>10,000	22 ± 3.6	182 ± 13	>1000	237 ± 52

DOTA: 1,4,7,10-tetraazacyclodecane-1,4,7,10-tetraacetic acid; DOTALAN: DOTA-lanreotide; DOTANOC: DOTA-l-Nal3-octreotide; DOTATATE: DOTA-Tyr3-octreotate; DOTATOC: DOTA-Tyr3-octreotide; DTPA: Diethylene triamine pentaacetic acid.
Data taken from [35] and, for Ga-DOTANOC, from [44].

tracers. In contrast to the radioisotopes ^{18}F and ^{64}Cu, which are cyclotron produced, ^{68}Ga has the advantage of being produced by a generator, making it more easily available. A rationale for using ^{64}Cu instead of ^{68}Ga, however, is its longer half-life (12.7 h vs 68 min.) and lower positron energy and thus short positron range (maximal energy of positrons [E_{max,β^+}] 0.58 MeV and maximal positron range [R_{max}] <3 mm vs E_{max,β^+} 1.90 MeV and R_{max} 9 mm), which might give it some advantages, even though the higher percentage of β-radiation may favor ^{68}Ga as a PET tracer (88 vs 19%).

Anderson *et al.* used the triethylenetetramine chelator to combine octreotide and ^{64}Cu. Compared with ^{111}In-DTPA-OC, more lesions were found in two out of eight patients using ^{64}Cu-triethylenetetramine-octreotide [42].

Pfeifer *et al.* used the DOTA chelator to chelate Tyr^3-octreotate and ^{64}Cu. A high and quite stable maximum SUV (SUV_{max}) for lesions on both early (1 h) and delayed (3 h) images suggested a high rate of tracer internalization and a low dissociation rate of ^{64}Cu-DOTATATE from somatostatin receptors during this time interval. SUV stability illustrated sufficient *in vivo* stability of the tracer for imaging purposes, even though some ^{64}Cu dissociation was seen in the liver. Compared with ^{111}In-DTPA-OC SPECT, additional lesions were found in six out of 14 patients (43%) [43]. Most notably, imaging was attained using a dose that gave only half the radiation burden compared with ^{111}In-DTPA-OC.

From a physical point of view, ^{18}F constitutes the ideal radionuclide for PET, due to its high amount of positron emission (97%), low positron energy and short positron range (E_{max,β^+} 0.63 MeV and R_{max} <3 mm), which is comparable with that of ^{64}Cu. Meisetschläger *et al.* tested the somatostatin receptor tracer Gluc-Lys(^{18}F-fluoropropionyl)-Tyr3-octreotate [^{18}F-FP]-TOCA) in a direct comparison to ^{111}In-DTPA-OC in 16 NET patients. Gluc-Lys(^{18}F-FP)-TOCA detected more than twice as many lesions and was rapidly taken up in the tumors, reaching 80% of the maximum tumor-to-background ratio at 16 ± 6.9 min after injection. The tumor-to-background ratio in the liver was 4.2 ± 2.0 at 60 min and thus comparable with ^{68}Ga-DOTATOC. The main drawback of Gluc-Lys(^{18}F-FP)-TOCA is its time-consuming multistep radiosynthesis and its limited overall yield [45].

Whether the differences in affinity among the tracers are important for imaging NETs also depends on the amount and distribution of somatostatin receptor in the normal tissue from which the tumors have to be differentiated.

• Physiological uptake of somatostatin receptor PET tracers

It is well known that SUVs are highly dependent on scanner resolution and image reconstruction techniques and may differ significantly between departments [46]. Absolute values of uptake in normal tissues of the different tracers are therefore difficult to compare unless performed by the same department, and no such data exist in the literature. Physiological uptakes for each of the most commonly used tracers have, however, been examined separately [47–49].

The ratios between tumor and normal tissue are of major importance in order to achieve optimal imaging. These ratios have been evaluated for ^{68}Ga-DOTATOC and ^{68}Ga-DOTANOC [47,48]. The scanning details and results are shown in **Table 2**.

Rather high physiological uptake is seen in the spleen and kidneys for all three tracers and in the adrenal and pituitary gland as well, especially with ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC. Of special importance is the physiological uptake in the liver, bone and normal pancreas due to the predominant localizations of NETs and metastases to

these organs. The uptake ratio between NET and normal tissue in the liver is approximately 3 for both ^{68}Ga-DOTANOC and ^{68}Ga-DOTATOC, and even higher (~10) in bones. Thus, good conditions were found for the imaging of NETs in these organs. The discrimination between NET and normal pancreatic tissue, especially in the processus uncinatus, has been much debated, and definitions of absolute SUV cut-off values in order to define tumor against normal tissue have been suggested by some [47,48], but not found to be practicable by others [50]. In 76 out of 103 scans, Krausz *et al.* found 97 sites of ^{68}Ga-DOTANOC uptake in the pancreas [50]. A total of 38 sites were judged to be due to physiological uptake, and 31 of these were in the processus uncinatus. Thus, tracer uptake in the processus uncinatus of the pancreas must be interpreted with caution. Cut-off values would be the perfect tool for diagnostic imaging, but they can seldom be defined and are not used in the clinical routine.

Performance of the somatostatin receptor PET tracers

A comparison of the sensitivity, specificity and usefulness of the different tracers in the

Table 2. Uptake of most used somatostatin receptor PET tracers in normal tissues and neuroendocrine tumors.

Parameter	^{68}Ga-DOTANOC [48]	^{68}Ga-DOTATATE [49]	^{68}Ga-DOTATOC [47]
Patients (n)	89	250	249
Dose and preparation	80–160 MBq iv., 1.5 l water equivalent contrast (gastrografin) orally	120–220 MBq iv. + 20 mg furosemid, 1.5 l water orally	68–220 MBq iv., full-dose, contrast-enhanced CT on most
Scan protocol	Scan 60–100 min PI, 2–3 min/bed	Scan 60–80 min PI, 3 min/bed	51–148 min PI, 2 min/bed
PET/CT used	Biograph™ Duo (Siemens Medical Solutions, Germany)	Biograph 64 TruePoint™ PET/CT scanner, 3D mode (Siemens Medical Solutions)	Discovery™ 690, 3D mode (GE Healthcare, WI, USA)
Uptake	***^{68}Ga-DOTANOC***[†]	***^{68}Ga-DOTATATE***[†]	***^{68}Ga-DOTATOC***[†]
Liver:			
– Normal	6.9 ± 2.0	6.5 ± 2.2	12.5 ± 4.0
– Metastases	19.6 ± 13.4	NR	29.8 ± 16.5
– Ratio[‡]	3.4 ± 2.3	NR	2.8 ± 1.6 (4.7 at 90 min)
Bone:			
– Normal	0.8 ± 0.3	1.0 ± 0.3	1.9 ± 0.8
– Metastases	9.5 ± 6.0	NR	19.8 ± 18.8
– Ratio	11.3 ± 8.9	NR	10.5 ± 14.2
Pancreas:			
– Processus uncinatus	5.8 ± 2.0	6.5 ± 2.2	10.5 ± 4.1
– Primary tumor	20.8 ± 10.8	NR	33.6 ± 14.1
– Ratio	NR	NR	5.2 ± 2.8
Muscle:			
– Normal	1.0 ± 0.3	NR	2.3 ± 1.0
Lymph node:			
– Metastases	12.5 ± 10.0	NR	NR
Spleen:			
– Normal	22 ± 10.0	18.9 ± 6.6	32.6 ± 11.8
GI:			
– Normal	2.6 ± 1.0	NR	4.7 ± 1.9
Pituitary gland:			
– Normal	2.6 ± 1.3	11 ± 4.5	8.0 ± 3.5
Adrenal glands:			
– Normal	6.0 ± 2.5	14 ± 5.6	16.3 ± 5.8
Kidneys:			
– Normal	12.9 ± 3.8	14.2 ± 3.6	20.4 ± 7.7

[†]Uptake expressed as mean ± standard deviation of maximum standardized uptake values.
[‡]Ratio between tumor and normal tissue.
CT: Computed tomography; DOTANOC: DOTA-I-NaI3-octreotide; DOTATATE: DOTA-Tyr3-octreotate; DOTATOC: DOTA-Tyr3-octreotide; GI: Gastrointestinal; iv.: Intravenously; NR: Not reported; PI: Postinjection.

diagnosis of NETs is difficult to extract from the existing literature. Direct head-to-head comparison of the tracers in the same patients are sparse. Most studies have been performed with one tracer at a time and in heterogeneous patient groups, including many different NET types and localizations.

The approach to defining the gold standard for detecting existing disease – the crucial factor for determining sensitivity and specificity – also varies between studies. Different approaches have been used. The most common is the patient-based approach, testing whether the tracer detects disease in the patient or not. This is quite an approximate estimate and may be clinically insufficient since the presence of metastases in different regions is very important for the choice of treatment. Some have tried to compensate for this by dividing detected lesions into clinically relevant regions in order to assess the clinical impact of additional findings. Others have looked into every single lesion in order to determine the differences between two tracers or modalities. The approach with multiple lesions in every patient leaves the problem of verifying them all. It is not ethically reasonable to achieve histological confirmation of every lesion, so CT and/or MRI have mostly been used in order to confirm or exclude the positive PET findings. Buchmann *et al.* used CT and MRI only for positive verifications of lesions detected by PET, since the sensitivity might be higher for the PET modality than CT or MRI [23]. Many studies use a follow-up period of a certain length in order to verify the presence or absence of disease. This may be the best approach to reaching a gold standard; however, in slow-growing tumors, the follow-up period needs to be quite long. An important factor is the heterogeneity of tumors is their varying receptor profiles. For instance, there will be a large difference in the sensitivity of somatostatin receptor PET tracers used to detect insulinomas that are known to express lower amounts of sst2 compared with small intestinal NETs, which virtually all express sst2 [51].

In **Tables 3–5**, the diagnostic performance of the three most commonly used somatostatin receptor PET tracers are listed.

• Head-to-head comparison of the somatostatin receptor PET tracers

In only five studies have direct comparisons of two PET tracers using the same patient population been performed [59,60,67–69]. Poeppel *et al.* examined 40 NET patients with both ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE [67]. Using ^{68}Ga-DOTATOC, they found 262 CT-verified lesions compared with 254 found by ^{68}Ga-DOTATATE. Comparing the two scans lesion to lesion, the standardized maximum uptake was higher overall with ^{68}Ga-DOTATOC than ^{68}Ga-DOTATATE, in addition to when the values were normalized to liver or muscle tissue. However, the tumor uptake varied considerably both within and between the patients. In addition to 18 patients with lesions displaying the highest uptake on ^{68}Ga-DOTATOC, 18 patients showed a mixture of lesions with either the highest uptake on ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC, while lesions only showing the highest uptake on ^{68}Ga-DOTATATE were found in four patients [67]. The presence of sst5 in the group of NETs displaying higher values with ^{68}Ga-DOTATOC might explain these results. When dividing all of the lesions into eight regions and counting the regions with at least one positive lesion, there was no significant difference between ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC, making the differences less clinically relevant.

Kabasakal *et al.* have compared the detection of NET lesions in a head-to-head comparison of ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC in 20 patients **(Tables 4 & 5)** [59]. ^{68}Ga-DOTATATE detected 130 lesions while ^{68}Ga-DOTANOC detected 116 lesions, but this was not significantly different. Sensitivity on a patient level was calculated to be equally high at 93% in both scans, and the specificity was 100%. The amount of tracer in the lesions was significantly higher in ^{68}Ga-DOTATATE compared with ^{68}Ga-DOTANOC ($p < 0.05$) [59]. This is in concordance with the nearly ten-times higher affinity of ^{68}Ga-DOTATATE towards sst2 and emphasizes that additional affinities for sst3 or sst5 do not add to the performance of the tracer in this mixed NET patient population.

Wild *et al.* also compared ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC directly **(Tables 4 & 5)** [60]. Both of the tracers correctly identified 17 out of 18 patients with verified NETs. On a lesion-based analysis, ^{68}Ga-DOTANOC performed significantly better, detecting 238 out of 248 lesions compared with 212 out of 248. ^{68}Ga-DOTANOC showed a lower uptake in normal liver compared with ^{68}Ga-DOTATATE, and the additional lesions that were found were mainly due to detecting more liver lesions. ^{68}Ga-DOTATATE, however, detected more bone lesions. ^{68}Ga-DOTANOC found

Table 3. Sensitivity and specificity of ^{68}Ga-DOTATOC PET in neuroendocrine tumor patients.

Study (year)	Patients (n)	Lesions (n)	Injected activity (MBq)	Postinjection time (min)	Tumor type	Reference used	Patients (lesions/regions), n				Sensitivity (%); 95% CI†	Specificity (%); 95% CI†	Ref.
							TP	*FP*	*TN*	*FN*			
Hofmann *et al.* (2001)	8	40	80–250	0–84 dyn.	Carcinoids (two lungs, eight abdominal)	40 predefined lesions on CT or MRI (1–3 cm)	8 (40)	0 (0)	0 (0)	0 (0)	100; 63–100 (100; 91–100)	–	[25]
Koukouraki *et al.* (2006)	22	74	150–230	0–60 dyn.	Metastatic NETs	Needle biopsy, MRI and/or CT, clinical follow-up	21 (72)	0	0	1 (2)	96; 78–99 (97; 91–100)	–	[52]
Buchmann *et al.* (2007)	27	83	100–228	45	15 GEP, eight CUP, one pulmonary, three other	CT, MRI, histology, 13 regions not verified	27 (70)	0 (?)	0 (?)	0 (?)	100; 87–100	–	[23]
Gabriel *et al.* (2007)	84	NR	100–150	100	50 GEP, nine CUP, six pulmonary, 19 other	All available data (CT, MRI, histology, NaF	69	1	12	2	97; 90–100	92; 64–100	[26]
Putzer *et al.* (2009)	51	NR	150	60–90	Bone metastases only (34 GEP, ten CUP, five pulmonary, two other)	Bone scintigraphy (^{99m}Tc-dicarboxy propane diphosphonate or ^{18}F-NaF), follow-up	37	1	12	1	97; 87–100	92; 86–99	[53]
Versari *et al.* (2010)	19	28	1.5–2/kg	60	Duodenopancreatic NETs	EUS, MDCT, >6 months follow-up for negative lesions	12 (20)	1 (1)	5 (5)	1 (3)	92; 64–100 (87; 68–97)	83; 66–92 (83; 41–99)	[54]

†95% CIs calculated by [55].
CT: Computed tomography; CUP: Cancer of unknown primary; dyn.: Dynamic; EUS: Endoscopic ultrasonography; FN: False negative; FP: False positive; GEP: Gastro–entero–pancreatic; MDCT: Multidetector computed tomography; NET: Neuroendocrine tumor; NR: Not reported; TN: True negative; TP: True positive.

Table 4. Sensitivity and specificity of ^{68}Ga-DOTATATE PET in neuroendocrine tumor patients.

Study (year)	Patients (n)	Lesions/ regions (n)	Injected acitivty (MBq)	Postinjection time (min)	Tumor type	Refrence used	Patients (lesions/regions), n				Sensitivity %; 95% CI†	Specificity %; 95% CI†	Ref.
							TP	*FP*	*TN*	*FN*			
Kayani *et al.* (2008)	38	NR	120–200	45–60	28 GEP, six pulmonary, four CUP	Histology, FDG	31	0	0	7	82; 66–92	–	[56]
Kayani *et al.* (2009)	18	NR	120–200	45–60	18 pulmonary	Histology, follow-up, FDG	13	0	0	5	72; 47–90	–	[57]
Haug *et al.* (2009)	51	55 regions	200	60	Metastatic NETs (nine gastrointestinal, five pancreatic, six pulmonary, one other, five CUP	Lesions confirmed by CECT and follow-up	24 (54)	0	0	1 (1)	96; 81–99 (98; 90–100)	–	[58]
Srirajaskanthan *et al.* (2010)	25	47 regions, 226 lesions	120–200	60	NETs equivocal or negative on ^{111}In-DTPA-OC	Lesions confirmed by CT or MRI	41 (168)	0	4	6 (58)	87; 74–95 (74; 68–80)	–	[27]
Kabasakal *et al.* (2012)	20	NR	110–200	30–60	Eight CUP, five pancreatic, two pulmonary, two gastrinomas, two paragangliomas, one MCC, eight G2, one G3, one MANEC, two unknown	Negative patients controlled by MRI, CT and US	14	0	5	1	100; 40–100 (93; 680–99)	100; 48–100	[59]
Wild *et al.* (2013)	18	248 lesions	135–170	54–73	GEP (four G1seven G2, seven G3)	Confirmed by CT or MRI or FDG	17 (212)			1 (36)	94; 73–100 (85; 80–90)	–	[60]

†95% CIs calculated by [55].

CECT: Contrast-enhanced computed tomography; CT: Computed tomography; CUP: Cancer of unknown primary; DTPA-OC: DTPA-octreotide; FDG: Fluorodeoxyglucose; FN: False negative; FP: False positive; G1: WHO grade 1; G2: WHO grade 2; G3: WHO grade 3; GEP: Gastro–entero–pancreatic; MANEC: Mixed adenoneuroendocrine carcinoma; MCC: Merkel cell carcinoma; NET: Neuroendocrine tumor; NR: Not reported; TN: True negative; TP: True positive; US: Ultrasonography.

seven out of eight pancreatic NETs, whereas ^{68}Ga-DOTATATE found only three [60].

In a study by Putzer *et al.*, the new PET tracer ^{68}Ga-DOTA-lanreotide (DOTALAN) was used in order to elucidate whether 38 patients who, despite clinical sign of progression but had not qualified for PRRT by ^{68}Ga-DOTATOC, could benefit from PRRT using ^{90}Y-labeled lanreotide [68]. The tumor-to-background ratios calculated from SUV_{max} measurements were significantly higher for ^{68}Ga-DOTATOC, and ^{68}Ga-DOTATOC revealed significantly more tumor sites than ^{68}Ga-DOTALAN (106 vs 53). In eight of the patients who underwent both scans, the primary tumor was a thyroid tumor, and six out of eight had a higher SUV_{max} using ^{68}Ga-DOTALAN, perhaps demonstrating thyroid NETs being more prone to PRRT when using DOTALAN [68].

^{68}Ga-DOTALAN was compared with ^{68}Ga-DOTATATE in a study by Demirci *et al.* [69]. A heterogeneous group of 11 NET patients and one meningioma patient was compared lesion by lesion. Together, the two scans revealed 67 lesions. A total of 63 lesions were found by ^{68}Ga-DOTATATE, while only 23 lesions were found by ^{68}Ga-DOTALAN. There was a higher amount of physiological uptake in the bone marrow with ^{68}Ga-DOTALAN, and furthermore, the tumor lesions had a higher uptake of ^{68}Ga-DOTATATE in general [69].

Comparison of ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC is currently being undertaken in our department, but results are not yet available. However, by comparing the image quality and resolution, ^{64}Cu-DOTATATE seems promising **(Figure 2)**. Greater detail is obtained with the use of ^{64}Cu-DOTATATE, probably due to the difference in positron range as described earlier. The inhomogeneous uptake in the large liver metastasis seen on the ^{64}Cu-DOTATATE scan might be interpreted as necrotic tissue and these details are not as clearly seen on the ^{68}Ga-DOTATOC scan.

• Performance of the individual somatostatin receptor PET tracers

In 2012, Treglia *et al.* published a meta-analysis on the diagnostic performance of ^{68}Ga-labeled PET scans in 567 cases of thoracic and GEP NETs [70]. The pooled sensitivity and specificity values of ^{68}Ga-labeled somatostatin receptor PET tracers (irrespective of tracer type) for detecting GEP or thoracic NETs were 93% (91–95%) and 91%

Table 5. Sensitivity and specificity of ^{68}Ga-DOTANOC PET in neuroendocrine tumor patients.

Study (year)	Patients (n)	Lesions (n)	Injected activity (MBq)	Postinjection time (min)	Tumor type	Reference used	Patients (lesions/regions), n				Sensitivity (%); 95% CI†	Specificity (%); 95% CI†	Ref.
							TP†	*FP*	*TN*	*FN*			
Ambrosini *et al.* (2008)	13	NR	185	60	11 GEP, two pulmonary	Follow-up, seen on two imaging modalities	13	0	0	0	100; 73–100	–	[61]
Ambrosini *et al.* (2009)	11	NR	185	60–90	Pulmonary	CT, MRI, follow-up, histology	9	0	2	0	100; 66–100	100; 16–100	[62]
Ambrosini *et al.* (2010)	223	NR	120–185	60	Confirmed NETs – bone metastases only	Compared with CT and follow-up	44	0	179	0	100; 92–100	100 ; 98–100	[63]
Naswa *et al.* (2011)	109	P: 69; M: 77	132–222	45–60	GEP	CT, MRI, US, EUS, biochemical markers, follow-up	P: 54; M: 75	P: 3; M: 0	P: 37; M: 32	P: 15; M: 2	P: 78; 67–87; M: 97; 91–100	P: 93; 80–98; M: 100; 89–100	[64]
Krausz *et al.* (2011)	19	NR	83–184	56–96	Eight carcinoids, nine pancreatic, two CUP	CT, MRI, EUS, histology	19	0	0	0	100; 82–100	–	[22]
Naswa *et al.* (2013)	25	NR	130–222	45–60	Clinical gastrinomas, negative or equivocal on CT	Clinical status, biochemical gastrin (CgA)	17	0	0	8	68; 47–85	–	[65]
Kabasakal *et al.* (2012)	20	NR	110–200	30–60	Eight CUP, five pancreatic, two pulmonary, two gastriomas, two paraganglioms, one Merckel cell carcinoma (eight G1, eight G2, one G3, one MANEC, two unknown)	Negative controlled by MRI, CT and US	14	0	5	1	93; 70–99	100; 48–100	[59]
Ambrosini *et al.* (2012)	1239	NR	120–185	60	670 GEP, 311 non-GEP, 81 CUP, 65 general syndroms, 112 no NET confirmed	Biopsy, surgery, follow-up	652	9	524	54	92; 90–94	98; 97–99	[66]
Wild *et al.* (2013)	18	248	130–170	60–74	GEP (four G1, seven G2, seven G3)	Confirmed by CT, MRI or FDG	17 (232)	0	0	1 (16)	94; 73–100 (94; 89–96)	–	[60]

†95% CIs calculated by [55].

CT: Computed tomography; CUP: Cancer of unknown primary; EUS: Endoscopic ultrasonography; FDG: Fluorodeoxyglucose; FN: False negative; FP: False positive; G1: WHO grade 1; G2: WHO grade 2; G3: WHO grade 3; GEP: Gastro–entero–pancreatic; M: Metastases; MANEC: Mixed adenoneuroendocrine carcinoma; NET: Neuroendocrine tumor; NR: Not reported; P: Primary; TN: True negative; TP: True positive; US: Ultrasonography.

(82–97%), respectively. Looking at the performances of the tracers individually, the sensitivity of ^{68}Ga-DOTATOC (Table 3) for the patient-based studies was 92–100% and the specificity was 83–100%. For ^{68}Ga-DOTATATE (Table 4), the sensitivity seemed to be a little lower at 72–96%, and the specificity was only reported in a few studies to 100%. For ^{68}Ga-DOTANOC (Table 5), the sensitivity ranged from 68 to 100% and the specificity from 93 to 100%.

Taken together, no clear picture of the better performance of one tracer is obvious. However, there could be differences between specific NET types, as they express varying amounts of somatostatin receptor subtypes. The heterogeneity of the tumors in most of the studies can be seen from the tables. However, some studies are focused on specific tumor types and are thus more reliable for the specific type.

• Somatostatin receptor PET tracers for different types of NETs

GEP NETs

In 2011, Naswa *et al.* published results from 109 patients with GEP NETs examined with ^{68}Ga-DOTANOC and with the use of all common imaging modalities, biochemichal markers and follow-up as references (Table 5) [64]. Metastases were seen in 77 patients and the sensitivity and specificity values were high for these (97 and 100%, respectively), whereas the sensitivity was only 78% for the primary tumors, with a specificity of 93%. Other smaller studies have found sensitivity values on 94–100% for GEP NETs [60,61].

^{68}Ga-DOTATOC showed 100% sensitivity for the eight GEP NET patients included in a study by Hofmann *et al.* in 2001 [25], and 97% sensitivity for the 50 GEP NET patients included in a study by Gabriel *et al.* [26]. Versari *et al.* found a sensitivity of 92% and a specificity of only 83% in 19 patients with duodenopancreatic NETs using ^{68}Ga-DOTATOC (Table 3) [54]. These results might be explained by the previously mentioned difficult interpretations of uptake in the normal pancreatic tissue. In 25 patients with clinically defined gastrinomas with equivocal or negative findings on CT, Naswa *et al.* reported a sensitivity of 68% using ^{68}Ga-DOTANOC [65].

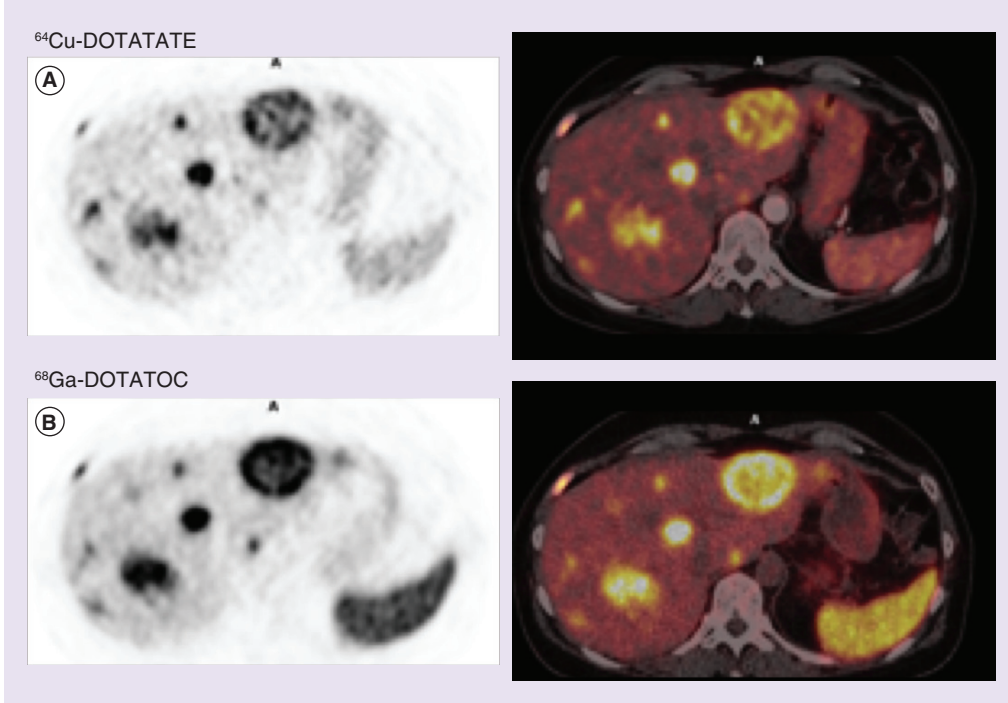

Figure 2. Imaging of the same neuroendocrine tumor liver lesions with ^{64}Cu-DOTA-Tyr3-octreotate and ^{68}Ga-DOTA-Tyr3-octreotide. (A) ^{64}Cu-DOTATATE; **(B)** ^{68}Ga-DOTATOC. Please note the greater detail in ^{64}Cu-DOTATATE images, probably due to differences in the positron ranges of ^{64}Cu. DOTATATE: DOTA-Tyr3-octreotate; DOTATOC: DOTA-Tyr3-octreotide.

Lung NETs

The distribution of somatostatin receptors in bronchial carcinoids was studied by Reubi and Waser [51]. sst1 and sst2 were detected in 70% of tumors. sst2 had the highest density, sst3 and sst4 were virtually undetected and sst5 was found in 20% and with low density. This distribution might favor the use of DOTATATE, since it is the somatostatin analog with the highest sst2 affinity.

Kayani *et al.* examined 18 pulmonary NET patients with ^{68}Ga-DOTATATE and found a sensitivity of only 72% **(Table 4)** [57]. However, the false-negative tumors were all high-grade tumors that were positive on ^{18}F-fluorodeoxyglucose (FDG) scans, while the typical bronchial carcinoids had high and selective uptake [57]. Ambrosini *et al.* also found 100% sensitivity and specificity for ^{68}Ga-DOTANOC in nine patients with typical, well-differentiated pulmonary NETs and two postoperation patients without tumors **(Table 5)** [62]. Using ^{68}Ga-DOTATOC, Jindal *et al.* showed that typical carcinoids had a higher uptake than atypical ones, and additional lesions that were not seen on CT were found as well [71].

Thus, all three of the tracers had an equally high sensitivity for the typical bronchial carcinoids, while only some of the high-grade tumors were visualized and had a lower uptake of tracer.

Liver metastases

The extent of liver metastasis is often a determinant for the choice of treatment. Options such as chemoembolization, surgical liver resection, radionuclide treatment or liver transplantation are highly dependent on the amount and localization of liver metastases.

The amount of physiological uptake of a tracer in the liver might make a difference between the performances of the different somatostatin receptor PET tracers. However, the ratio between tumor and normal tissue uptake was approximately 3 for both ^{68}Ga-DOTANOC [48] and ^{68}Ga-DOTATOC **(Table 2)** [47]. In one of the few direct comparison studies, when using ^{68}Ga-DOTANOC, Wild *et al.* detected significantly more liver lesions than when using ^{68}Ga-DOTATATE, and the tumor-to-background ratios were calculated to be 2.7 and 2.0, respectively **(Tables 4 & 5)** [60].

Bone metastases

The gold standard for detecting bone metastases is either with ^{99m}Tc-dicarboxy propane diphosphonate or the PET tracer ^{18}F-NaF. The detection of bone metastases is important since they are associated with poorer prognosis [72], and extended surgery is contraindicated in patients with known bone metastases [73].

Putzer *et al.* scanned 51 patients with ^{68}Ga-DOTATOC and a conventional bone scintigraphy (^{99m}Tc-dicarboxy propane diphosphonate) or ^{18}F-NaF **(Table 3)** [53]. ^{68}Ga-DOTATOC proved to be more accurate than both CT and bone scintigraphies. The sensitivity of ^{68}Ga-DOTATOC for detecting bone metastases was 97% and the specificity was 92%. The conventional bone scans did not reveal any additional bone metastases in any patients compared with ^{68}Ga-DOTATOC [53].

Ambrosini *et al.* detected 44 patients with bone metastases among 223 patients with confirmed NETs using ^{68}Ga-DOTANOC versus 35 patients when using CT alone **(Table 5)** [63]. With the incorporation of follow-up as a reference, sensitivity and specificity values of 100% were found [63].

Gabriel *et al.* compared ^{68}Ga-DOTATOC with ^{99m}Tc-hydrazinonicotinyl-Tyr(3)-octreotide (HYNIC-TOC) and/or ^{111}In-DTPA-OC and CT in 84 patients and found a significantly better overall diagnostic efficacy with ^{68}Ga-DOTATOC ($p = 0.001$) **(Table 3)** [26]. The difference in the detection rate was most pronounced for bone metastases. Of 116 ^{68}Ga-DOTATOC PET-positive bone lesions, SPECT delineated 84 lesions (72.5%) and CT delineated only 58 lesions (50%) [26].

In a lesion-to-lesion analysis in 18 patients scanned with both ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE, Wild *et al.* reported ^{68}Ga-DOTATATE to detect significantly more bone lesions compared with ^{68}Ga-DOTANOC (89 vs 82) **(Tables 4 & 5)** [60]. ^{68}Ga-DOTATATE had a lower bone marrow activity than ^{68}Ga-DOTANOC, resulting in a higher tumor-to-background activity for bone metastases with ^{68}Ga-DOTATATE.

Unknown primaries

A well-known situation involves finding metastases of the liver as the first clinical presentation of NETs without any evidence of the primary tumor. In a study by Prasad *et al.*, 59 NET patients with unknown primary tumors were scanned with ^{68}Ga-DOTANOC PET/CT [74]. The primary tumor site was localized in 35 out of 59 patients (59%), while CT alone only

found 12 out of 59 primary tumor sites (20%). Thus, PET found almost three-times as many primary tumor sites as CT alone [74]. Similar results were obtained by Naswa *et al.* with ^{68}Ga-DOTANOC, which found 12 out of 20 primary tumors (60%) in NET patients with unknown primary tumors [75]. Furthermore, they found a significant correlation between the primary tumor SUV_{max} and the SUV_{max} of their metastases [75].

Using ^{68}Ga-DOTATATE, Lapińska *et al.* found the primary tumor in five out of 14 patients (36%) with unknown primary cancers [76]. No direct comparisons of the efficacy for identifying unknown primary tumors between the tracers have been published. A quantitative determination of the amount of the different somatostatin subtypes in the identified metastases of an unknown primary NET could potentially help us to determine what tracer is most likely to be most sensitive in individual cases. This requires that metastases and primary tumors show the same phenotypes.

Unusual NETs

Somatostatin receptor PET with ^{68}Ga-DOTANOC has been described in a small series of rare NETs [77]. ^{68}Ga-DOTANOC was positive, showing at least one positive lesion in seven out of 14 cases. It was considered useful in 12 out of 14 cases, but it was considered inconclusive in two cases, one of uterine and one of ovarian localization. The useful cases included three paragangliomas (all positive), three prostate NETs (one positive and two negative), two uterine cases and a single breast, lymphoma, ear and kidney NET.

Impact on clinical decision-making

The crucial question whenever a new diagnostic modality is evaluated is whether there is a clinical impact on treatment, control or prognosis for patients. The use of somatostatin receptor PET scanning as an addition to conventional imaging by CT or MRI changed treatment in 20–60% of cases [64,78,79], especially those concerning the choice of treatment with PRRT [80]. There is therefore no doubt that NET patients benefit from the use of somatostatin receptor PET imaging. No studies have determined a significant clinical gain of using one tracer over the others among the most used tracers – ^{68}Ga-DOTATOC, ^{68}Ga-DOTATE and ^{68}Ga-DOTANOC.

Dosimetry & the best time to scan

In the process of selecting the optimal tracer for somatostatin receptor imaging, the amount of radiation given to the patient should also be considered, especially since NET patients often receive multiple scans during their lifetime. Differences in radionuclide, affinity and excretion of the somatostatin receptor tracers also lead to variable radiation burden to the patients. A comparison of absorbed doses in the most exposed organs and the effective doses for the whole body is shown in **Table 6** for the most commonly used and one promising new tracer [43,81–86].

For ^{68}Ga-emitting somatostatin receptor tracers, the most exposed organ is the spleen, followed by the bladder, kidneys and liver. The primary excretion route is renal. For ^{64}Cu-DOTATATE, uptake in the spleen is lower compared with its ^{68}Ga counterparts (see **Figure 2**); instead, the liver seems to be more exposed [43]. All of the somatostatin receptor PET tracers possess a dosimetric advantage for the patient compared with the γ-emitting tracers ^{111}In-DTPA-OC and ^{111}In-DOTATOC, both of which result in approximately twice the radiation dose to the patients **(Table 6)** [86].

The scan times used for ^{68}Ga-PET somatostatin receptor tracers are 30–100 min after the injection of the tracer. This allows sufficient time for the tracer to accumulate in the tumors and background clearance, taking the short half-life of ^{68}Ga (68 min) into account [24,26]. If ^{64}Cu-coupled tracers are used, the possibility of later imaging exists, because of its longer half-life (12.7 h). Scans from 1 to 24 h postinjection have been evaluated, and late scans might give some additional findings in selected cases [43].

Addition of anatomical imaging

Somatostatin receptor PET scanning is often performed together with a CT scan in order to provide anatomical information regarding the discovered lesions. Low-dose CT can be used to spare the patient from the full-dose radiation of a diagnostic CT scan, especially during long-term follow-up. For the initial diagnostic work-up, staging and treatment response, monitoring the highest accuracy must be pursued, and a diagnostic CT scan using a triple-phase CT protocol is recommended or, if possible, a combination of MRI and the PET modality could be used, since this gives very high accuracy.

Ruf *et al.* compared the sensitivities and accuracies of ^{68}Ga-DOTATOC and each of the three

Table 6. Absorbed doses in the most exposed organs and the effective doses of somatostatin receptor tracers.

Organ/dose	^{68}Ga-DOTANOC [81]	^{68}Ga-DOTATOC [82]	^{68}Ga–DOTATATE [83]	^{64}Cu-DOTATATE [43]	^{111}In-DTPAOC [86]	^{111}In-DOTATOC [86]
Kidneys (mGy/MBq)	0.09	0.22	0.09	0.14	0.47	0.50
Liver (mGy/MBq)	0.03	0.07	0.05	0.16	0.07	0.05
Spleen (mGy/MBq)	0.07	0.24	0.28	0.12	0.36	0.47
Bladder (mGy/MBq)	0.08	0.07	0.13	0.04	0.19	0.16
Effective dose (mSv/MBq)	0.02	0.02	0.03	0.03	0.05	0.05
Typical administed dose (MBq)	120–200	120–200	120–200	180–220	111–222	140–200
Radiation burden at a typical dose (mSv)	2.0–3.3	2.8–4.6	3.0–5.1	5.7–6.9	5.6–11.1	7.0–10.0

DOTANOC: DOTA-I-Nal3-octreotide; DOTATATE: DOTA-Tyr3-octreotate; DOTATOC: DOTA-Tyr3-octreotide.

scans from a triple-phase CT protocol in 51 NET patients [87]. PET proved to be the most accurate and robust submodality. For correct topographic assignment of the PET foci, the portal venous phase and venous phase showed comparable sensitivities and the arterial-phase CT was the least prominent, but the most robust. However, each of the scans showed exclusive foci detection and together delivered synergistic information [87]. Enhancement with contrast in a ^{68}Ga-DOTATOC PET/CT study increased the sensitivity from 92 to 99% [88].

The combination of PET with MRI increased the sensitivity for liver metastases (especially lesions of <1 cm) from 74 to 91%, and specificity was raised from 88 to 96% compared with PET/CT [89]. A combination of diffusion-weighted imaging (DWI) and contrast-enhanced MRI (with hepatocyte-specific contrast) improved the specificity [89]. In addition, Giesel *et al.* found more liver metastases with MRI compared with CT [90], while the two modalities of ^{68}Ga-DOTATOC/low-dose CT and ^{68}Ga-DOTATOC/MRI performed equally in a study by Gaertner *et al.* [91].

Further to strict anatomical information, additional information might be attainable from MRI due to functional features as DWI and spectroscopy both known to be prognostic in various cancer forms. We have seen several cases of NET liver metastases presenting highly different lesions on DWI and PET scans, and one case has been published [92]. For patients who are not suitable for imaging with contrast-enhanced CT, MRI seems promising for lesion detection [93].

The latest ENETS consensus guidelines state that a high-resolution, three-phase CT in combination with PET using a ^{68}Ga somatostatin receptor PET tracer should be performed in NET patients with unknown primary tumors. Furthermore, MRI is considered to be superior to CT in the detection and follow-up of liver metastases, so if the CT scan of liver metastases is inconclusive, T2-weighted, thin-slice, dynamic, gadolinium-enhanced MRI is recommended [30].

Comparisons with other PET tracers

• Comparison with ^{18}F-L-dihydroxyphenylalanine

Many neuroendocrine cells take up and decarboxylate amino acid precursors, such as L-dihydroxyphenylalanine (DOPA). This feature enables imaging with ^{18}F-DOPA. ^{18}F-DOPA scanning provides information regarding the biochemistry of the tumor, rather than how well it expresses somatostatin receptors. However, in a comparison between ^{68}Ga-DOTANOC and ^{18}F-DOPA in 13 patients with GEP NETs or lung NETs, the ^{68}Ga-DOTANOC scan detected 71 lesions compared with only 45 lesions being found by ^{18}F-DOPA PET scans [61]. In another study of 15 patients, ^{68}Ga-DOTANOC and ^{18}F-DOPA showed comparable results when matched on a patient basis, but on a lesion basis, ^{68}Ga-DOTANOC was again superior, even though the patients had NETs favoring amine precursor uptake and decarboxylation, such as pheochromocytomas, paragangliomas and medullary thyroid cancers [94].

Haug *et al.* found a patient-based sensitivity of 96% for ^{68}Ga-DOTATATE compared with 56% for ^{18}F-DOPA in 25 patients with well-differentiated metastatic NETs. However, a correlation between the SUV_{max} of ^{18}F-DOPA and plasma serotonin in patients who were positive for ^{18}F-DOPA was found, suggesting a role for ^{18}F-DOPA scans in serotonin-secreting tumors that are not visible on somatostatin receptor PET [58].

• Comparison with ^{18}F-FDG

^{18}F-FDG PET has recently been shown to provide prognostic information regarding survival from NETs [95]. Binderup *et al.* found 58% of 96 patients to be positive on ^{18}F-FDG PET [96]. These were mainly found in the group of patients with the highest-proliferating tumors (Ki-67 >15%); among these, 92% were FDG positive. Similarly, Kayani *et al.* found a significant correlation between the uptake of ^{68}Ga-DOTATATE or ^{18}F-FDG and histological tumor grade on histology [56]. In low-grade NETs, 97 lesions were found by ^{68}Ga-DOTATATE and no lesions were found by ^{18}F-FDG, while ^{18}F-FDG detected 72 lesions compared with no lesions by ^{68}Ga-DOTATATE in high-grade NETs.

Oh *et al.* investigated somatostatin receptor status and glucose metabolism in a group of patients with progressive, metastasized NETs [97]. Only approximately 60% of the lesions showed matching lesions as detected by both ^{68}Ga-DOTANOC and ^{18}F-FDG.

Wild *et al.* found that even though the SUV_{max} decreased for both ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE as the tumor grade increased, they both detected significantly more G3 lesions (82 and 90%, respectively) than ^{18}F-FDG PET (58%) [60].

Since the most aggressive NETs are often negative on somatostatin receptor imaging and often positive on ^{18}F-FDG PET, there may be a role for the diagnostic use of ^{18}F-FDG PET in somatostatin receptor imaging-negative cases.

Conclusion

It is now 25 years since γ-camera-based somatostatin receptor imaging was introduced and improved diagnosis and patient management in NETs. Recently, several PET tracers, most notably ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC, have been introduced as substitutes for γ-emitting tracers. The bulk of the literature has clearly proven that these PET tracers are superior to the γ-emitting ^{111}In-DTPA-OC. On the whole, the ^{68}Ga-based tracers perform similarly and so their choice is best made based on past experience and matching it with PRRT. Accordingly, evidence now supports the shift to somatostatin receptor PET tracers in the clinical routine, as has largely happened, especially in Europe. So far, ^{18}F-labeled somatostatin receptor tracers have not emerged at a larger scale. Two ^{64}Cu-based somatostatin receptor PET tracers have been described, most recently ^{64}Cu-DOTATATE. In theory, ^{64}Cu-labeled tracers should provide better resolutions than ^{68}Ga-labeled tracers, but whether this translates into improved diagnostic performance remains to be shown.

Future perspective

Somatostatin receptor imaging should be performed in PET whenever possible. Whereas the ^{68}Ga-based somatostatin analog tracers have paved the way for using PET instead of SPECT for somatostatin receptor imaging, we foresee that labeling with radionuclides such as ^{18}F and ^{64}Cu, as well as new ligands (e.g., receptor antagonists), will further improve the value and use of these tracers. In addition, tracers that specifically target subtypes of NET (e.g., GLP-1 for the imaging of insulinomas) may become routine in the future. Interesting results have been reported using an analog to the GLP-1 receptor, exendin 4, either coupled to ^{111}In or ^{68}Ga for imaging insulinomas [98–100]. Evidence that the somatostatin receptor and GLP-1 receptor distributions in benign and malignant insulinomas are different has been presented [101,102], and a greater sensitivity for detecting insulinomas overall might therefore be achievable with a combination of tracers in the same way as is observed with FDG and somatostatin receptor PET for poorly differentiated G3 NETs.

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EXECUTIVE SUMMARY

Neuroendocrine tumors

- Neuroendocrine tumors (NETs) have seen a fivefold increase in incidence since 1973.
- Lung (25%) and gastro–entero–pancreatic NETs (75%) are the most frequent.
- The overexpression of five different subtypes of somatostatin receptors is seen in 80–100% of NETs.

PET versus γ-cameras

- PET has a better sensitivity and resolution compared with imaging by SPECT.
- PET makes the quantification of tracer uptake possible.
- Lower radiation doses to the patients are possible when using PET tracers.
- Lower costs and greater patient comfort are possible with PET.

Somatostatin receptor PET tracers

- ^{68}Ga-DOTA-Tyr3-octreotide (DOTATOC), ^{68}Ga-DOTA-Tyr3-octreotate (DOTATATE) and ^{68}Ga-DOTA-l-Nal3-octreotide (DOTANOC) are the most frequently used tracers for somatostatin receptor PET.
- A few ^{18}F- or ^{64}Cu-labeled tracers have been tested.
- ^{68}Ga and ^{18}F have short half-lives (68 and 110 min, respectively), while ^{64}Cu (half-life: 12.7 h) makes late imaging possible.
- ^{18}F and ^{64}Cu have a shorter positron range than ^{68}Ga, which translates into better resolution.

Affinity of the somatostatin receptor PET tracers

- Ga-DOTATOC has affinity towards sst2 and sst5.
- Ga-DOTATATE only has affinity towards sst2. The affinity is tenfold higher than with Ga-DOTATOC or Ga-DOTANOC.
- Ga-DOTANOC has affinity towards sst2, sst5 and sst3. The affinity towards sst5 is tenfold higher than with Ga-DOTATOC.
- The most abundant receptor is sst2, which is expressed in 70–90% of NETs.

Head-to-head comparison: only a few such studies exist

- ^{68}Ga-DOTATATE versus ^{68}Ga-DOTATOC: patient- or region-based comparisons showed no differences.
- ^{68}Ga-DOTATATE versus ^{68}Ga-DOTANOC: ^{68}Ga-DOTATATE found fewer lesions in one study and more in another. Patient-based comparison showed no differences.
- ^{68}Ga-DOTALAN found fewer lesions than with ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE.

Performance of somatostatin receptor PET tracers: noncomparative studies

- Patient-based sensitivities for the three most used tracers are: ^{68}Ga-DOTATOC: 78–100%; ^{68}Ga-DOTATATE: 72–100%; and ^{68}Ga-DOTANOC: 68–100%.

Comparison with other PET tracers

- ^{18}F-L-dihydroxyphenylalanine found the fewest lesions in studies comparing it with ^{68}Ga-DOTANOC or ^{68}Ga-DOTATATE.
- ^{18}F-fluorodeoxyglucose (FDG) uptake is seen in high-grade lesions and not in low-grade lesions, which is the opposite in somatostatin receptor PET, making ^{18}F-FDG suitable for aggressive cases.
- ^{18}F-FDG provides prognostic information in NETs.

Conclusion & future perspective

- Somatostatin receptor imaging should be PET based.
- ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC all perform well and the choice is best made based on experience with the tracer and matching it with peptide receptor radionuclide therapy.
- ^{18}F- and ^{64}Cu-labeled somatostatin receptors have not emerged into routine practice so far. They have potential for a better resolution than with ^{68}Ga-labeled tracers.
- PET tracers using new somatostatin analogs as radioligands might improve affinity and sensitivity further.

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• of interest; •• of considerable interest

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